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CLINICAL & BASIC RESEARCH

Intrauterine Fetal Blood Transfusion

Descriptive study of the first four years' experience in Oman

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نقل الدم للجنين في داخل الرحم

دراسة وصفية لتجربة الأربعة سنوات الأولى في سلطنة عمان

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ABSTRACT: ***Objectives:*** Haemolytic disease of the fetus and newborn (HDFN) causes hydrops *fetalis*. The successful treatment of HDFN has been reported with intrauterine blood transfusion (IUT). This study aimed to describe the initial experience with IUT procedures in Oman. ***Methods:*** This retrospective observational study took place at the Royal Hospital and Sultan Qaboos University Hospital Blood Bank, Muscat, Oman, and included all women who underwent IUT procedures in Oman between March 2012 and March 2016. Gestational and neonatal outcomes were assessed, including complications, morbidity, neurodevelopmental *sequelae* and mortality. ***Results:*** A total of 28 IUT procedures for 13 fetuses carried by 11 women were performed. Gestational age at the time of referral ranged from 13–30 weeks, while the median gestational age at first IUT procedure was 26 weeks (range: 19–30 weeks). Indications for the procedure included HDFN caused by anti-D (n = 6), a combination of anti-D and anti-C (n = 4), anti-K (n = 1) and anti-Js^b (n = 1) antibodies and nonimmune hydrops *fetalis* due to a congenital parvovirus infection (n = 1). Median fetal haemoglobin levels at the beginning and end of the procedure were 4.6 g/dL and 12.8 g/dL, respectively. Most procedures were transplacental intravascular transfusions through the placental umbilical cord root (71.4%), followed by transamniotic intravascular transfusions (14.3%). The overall survival rate was 61.5%, with five deaths; of these, four were intrauterine and one was an early neonatal death due to non-resolved hydrops and severe cardiac dysfunction. ***Conclusion:*** As a relatively novel obstetric procedure in Oman, IUT seems to result in a favourable outcome for hydropic fetuses.

Keywords: Fetus; Hydrops Fetalis; Anemia; Intrauterine Blood Transfusion; Fetal Death; Oman.

الملخص: الهدف: مرض انحلال الدم لدى الأجنة وحديثي الولادة يسبب حالة تجمع للسائل الجنيني، وتؤشر التقارير السابقة عن علاج ناجح لهذا المرض باستخدام تقنية نقل الدم داخل الرحم، هدفت الدراسة الحالية إلى وصف التجربة الأولية لإستخدام هذه الطريقة في عمان. **الطريقة:** أجريت هذه الدراسة الإستعادية في المستشفى السلطاني وبنك الدم في مستشفى جامعة السلطان قابوس في مسقط، عمان، وشملت الدراسة جميع النساء اللواتي خضعن لعملية نقل الدم داخل الرحم في عمان بين شهر مارس 2012 ومارس 2016. تم خلال الدراسة تقييم نتائج الحمل وما بعد الولادة، وتضمّن ذلك المضاعفات اللاحقة، وتوابع التأثير على النمو العصبي، إضافة إلى رصد الوفيات. **النتائج:** تم إجراء 28 عملية نقل دم داخل الرحم، ل 13 جنين لأحد عشر أم حامل، تراوح عمر الحمل في وقت التحويل بين 30–13 أسبوعاً، في حين أن متوسط عمر الجنين في أول عملية نقل دم كان 26 أسبوعاً (المدى: 30–19 أسبوعاً)، شملت مستدعيات عمل هذا الإجراء الجراحي وجود مرض انحلال الدم الجنيني أو لحديثي الولادة الناتج عن أجسام مناعة مضادة من نوع مضاد D (عدد الحالات = 6)، ومزيج من مضاد D ومضاد C (عدد الحالات = 4)، أو مضاد K (عدد الحالات = 1) ومضاد Js^b (عدد الحالات = 1)، وكذلك الناتج عن تجمع السائل الجنيني الغير مناعي، بسبب إلتهاب فيروس الحميات الصغيرة الخلقي (عدد الحالات = 1). كان متوسط مستوى الهيموجلوبين الجنيني في بداية ونهاية الإجراء 4.6 غرام/ديسيلتر و 12.8 غرام/ديسيلتر، على التوالي، وكانت معظم إجراءات نقل الدم خلال المشيمة عبر الأوعية الدموية من خلال جذر الحبل السري المشيمي (71.4%)، تليها نقل داخل الأوعية خلال السائل السلوي (14.3%)، بلغ معدل البقاء على قيد الحياة 61.5%، مع خمس حالات وفاة؛ أربعة منهم داخل الرحم، وواحد منهم حديث الولادة وكانت الوفاة في وقت مبكر بعد عدم الاستجابة لعلاج تجمع السائل الجنيني وكذلك وجود خلل وظائفي في القلب. **الخلاصة:** يمكن اعتبار إجراء عملية نقل دم داخل الرحم المتسخدمة حديثا في سلطنة عمان، إجراء يساعد على الحصول على نتائج مفضلة للأجنة المصابين بحالة التجمع المائي الجنيني.

الكلمات المفتاحية: الجنين؛ تجمع السائل الجنيني؛ فقر دم؛ نقل الدم داخل الرحم؛ وفاة الجنين؛ عمان.

Advances in Knowledge

- *Intrauterine blood transfusion (IUT) is a new addition to obstetric management in Oman. This study found that the outcomes of this procedure in Oman were comparable to reported rates from pioneer studies in the literature.*
- *In Oman, the commonest indication for an IUT was anti-D haemolytic disease of the fetus and the newborn.*

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Application to Patient Care

- *As per the findings of this study, obstetricians in Oman need to prevent anti-D alloimmunisation by ensuring that anti-D prophylaxis is administered to Rhesus-negative mothers.*
- *Moreover, obstetricians need to be made aware of the availability of IUT facilities in the country to facilitate the early referral of high-risk cases before hydrops fetalis develops.*

Haemolytic disease of the fetus and newborn (HDFN) is caused by maternal allo-antibodies that actively cross the placenta to the fetal circulatory system during gestation and destroy fetal erythroid cells.[1] As a result, fetal anaemia, hydrops *fetalis* and intrauterine fetal death (IUFD) may occur. Currently, the prevention and treatment of HDFN is successful in most modern obstetric practices worldwide. The primary prevention of HDFN includes the antenatal and postnatal administration of anti-D immunoglobulin for Rhesus (Rh) D-negative mothers, while secondary prevention is achieved via antenatal screening for red blood cell (RBC) antibodies.[2]

One of the greatest breakthroughs in fetal medicine was the introduction of percutaneous intraperitoneal transfusions in the 1960s.[3] This was followed by intravascular intrauterine blood transfusions (IUTs), in which intravascular transfusions are performed using an ultrasound-guided needle inserted into the umbilical vein.[4–6] The treatment of fetal anaemia using IUT has been associated with survival rates that exceed 90% in specialised centres.[7–9] The main indication for an IUT is fetal anaemia due to RBC alloimmunisation, but the procedure is also considered in any fetal disease with severe anaemia, including parvovirus B19 infections and massive fetomaternal haemorrhage.[10] Nonetheless, the blood components needed for the IUT procedure must adhere to existing guidelines and recommendations.[11] The procedure is not free from risks, including a 1–2% rate of fetal loss.[11–13]

Prior to 2012, cases necessitating IUT in Oman were referred abroad due to a lack of certified fetal medicine specialists and necessary support services in the country. In March 2012, the first IUT procedure in Oman was performed on a patient with HDFN due to anti-D antibodies, thanks to collaboration between the Fetal Medicine Unit of the Department of Obstetrics & Gynaecology at the Royal Hospital and the Sultan Qaboos University Hospital (SQUH) Blood Bank in Muscat, Oman. This study aimed to describe the first four years' experience with IUT procedures in Oman, including indications for IUT and the gestational and neonatal outcomes of the procedures. To the best of the authors' knowledge, this is the first descriptive study of IUT procedures in Oman.

Methods

This retrospective observational study was conducted at the Royal Hospital and SQUH Blood Bank and included all women who underwent IUT in Oman between March 2012 and March 2016. Data were collected from the patients' records, including indications for the procedure, gestational age (including at the time of referral, at each IUT and at delivery), the number of procedures performed per pregnancy and the development of any procedure- or non-procedure-related complications, such as fetal bradycardia requiring an emergency Caesarean section (CS), cord haematomas, intrauterine death within one week of the procedure, intrauterine infections, premature rupture of the membranes (PROM) or spontaneous preterm labour before 32 gestational weeks.[14] Perinatal and neonatal mortality and morbidity and the development of postnatal neurodevelopmental *sequelae* was also determined.

At presentation, the patients' obstetric history was determined and fetal middle cerebral artery peak systolic velocity (MCA-PSV) was measured. In addition, blood group was determined and viral and antibody screening was performed. Subsequently, a decision was made as to whether an IUT procedure was needed and, if so, the volume of RBC units required. Fetal Doppler MCA-PSV measurements were used to determine the optimal timing of the first and second IUTs.[15] Cordocentesis was planned if the fetus had MCA-PSV values of ≥1.5 multiples of the median and/or signs of hydrops *fetalis* were detected via ultrasonography.[16] The transfusion was then performed if pre-IUT blood samples confirmed fetal anaemia. Decisions on subsequent IUTs were made after predicting the likelihood of continuing fetal anaemia, indicated by an expected haemoglobin (Hb) decrease of 0.3 g/dL per day from post-transfusion Hb measurements following the second IUT procedure.[17]

Once the decision to perform an IUT was made, a search for suitable blood donors was initiated. All blood donors selected were regular donors at the SQUH Blood Bank or the Department of Blood Bank Services at the Ministry of Health (MOH) in Oman. Selected donors fulfilled standard donor selection criteria and

had to have made a minimum of one previous donation negative for all serological markers within two years of the planned IUT. All potential donors were tested for the sickle cell trait, HIV-1 and -2, hepatitis C virus, hepatitis B virus (including surface antigen and anti-core antibodies) and syphilis. All RBC units used were of blood group O, RhD-negative, sickle-negative, negative for the corresponding antigens of the implicated HDFN-causing maternal antibodies and cross-match compatible with the maternal *sera*.[11] In addition, the donors were matched to the maternal Rh (C, c, E and e) and Kell (K) phenotype whenever possible.

Donated whole blood was collected in a citrate phosphate dextrose anticoagulant solution and processed at the SQUH Blood Bank based on a written protocol. None of the processed RBC units were suspended in a saline, adenine, glucose and mannitol additive solution. Prior to storage, processed RBC units were leukoreduced to a residual white blood cell (WBC) count of $<5 \times 10^6$/L. The RBC units were then haemoconcentrated by centrifugation in order to reach a haematocrit (Hct) proportion of 70–85%.[18] A saline wash was used for the processed RBC units of one previously reported patient with HDFN due to the presence of anti-Js^b antibodies; in this case, the mother had donated blood while pregnant due to the low likelihood of finding a suitable donor.[19]

All RBC units were quality-checked for final volume measurements, Hct proportion and residual WBC counts. After testing to determine the ABO blood group, the donor samples were additionally screened for Rh (C, c, E and e) and K antigens, the sickle cell trait and glucose-6-phosphate dehydrogenase deficiency. The RBC units were irradiated using a Cesium-based irradiation method to a minimum target dose of 25 Grays, as per existing recommendations.[11] An irradiation tag was attached to each unit to ensure the target dose of irradiation was delivered (RadTag® Irradiation Indicator, RadTag Technologies, Edmonton, Alberta, Canada). Finally, the RBC units were labelled before being issued. The volume of prepared RBC units for each patient was determined according to the obstetrician's orders. All components used in the IUT procedures were fresh, having been issued within 24 hours of donation from the SQUH or MOH blood banks.

A multidisciplinary team supervised all blood component and transfusion aspects of the IUT procedures, including two haematopathologists and a haematologist with expertise in transfusion medicine. All IUT procedures were performed by a fetal therapist at the Fetal Medicine Unit in the Royal Hospital using a prespecified protocol under aseptic conditions and employing continuous ultrasound guidance. The fetal therapist who performed the procedure had completed their fellowship training abroad. Each patient was given 5 mg of diazepam and intravenous prophylactic antibiotics prior to the procedure. In addition, antenatal steroids were administered to patient ≥25 gestational weeks, in case an emergency CS was necessary. Accordingly, all IUT procedures were performed in close proximity to an operating theatre. For the transfusion, a 20- or 22-gauge spinal needle was used while the patient was under local analgaesia. Prior to the transfusion, 1 mL of fetal blood was tested to assess baseline Hct proportion, complete blood count and reticulocyte count. If fetal anaemia was confirmed, the transfusion was performed at a rate of 5 mL/minute, with close fetal monitoring and targeting to raise the fetal Hct proportion to 45–50%, except in cases of hydrops *fetalis*. In hydropic fetuses, an exchange transfusion was performed. Alternatively, half of the estimated volume was transfused to avoid volume overload, followed by assessment of the fetus. A second procedure was planned 24–48 hours later so as to reach the target Hct proportion. The volume of the processed RBC units to be transfused was calculated as follows:[20]

$$RBC\ volume = \frac{(FPBV \times TH - IH)}{HTB}$$

where FPBV is the fetoplacental blood volume in mL, TH is the target Hct proportion, IH is the initial fetal Hct proportion and HTB is the Hct proportion of the transfused RBC unit. The fetoplacental blood volume was calculated from the ultrasound estimate of fetal weight (UEFW) in g according to the following formula:[20]

$$FPBV = 1.046 + UEFW \times 0.14$$

Immediately following the free return of blood, the fetus was paralysed using 0.3 mg/kg of pancuronium to reduce the risk of a catastrophic Wharton's jelly haematoma or dislodgement of the needle.[21] The umbilical vein at the site of the cord root into the placenta was targeted for the transfusion. A transplacental route was used for cases with an anterior placenta, while a transamniotic route was used in cases with a posterior placenta. An intracardiac route was chosen in cases in which it was technically difficult to reach the site where the umbilical cord connected to the placenta. None of the procedures were performed via an intrahepatic route or a free loop of the umbilical cord.

Once the transfusion was complete, post-transfusion Hb level and Hct proportion was checked. All patients >28 gestational weeks were monitored with fetal heart rate tracing for one hour following the procedure. Intervals between the procedures were determined based on weekly MCA-PSV Doppler assessments and

Table 1: Characteristics of intrauterine transfusions performed in Oman over a four-year period (N = 28)*

Characteristic	N
Maternal history	
Previous HDFN	10
Previous IUFD	6
Fetal presentation	
Hydrops *fetalis*	10
Fetal anaemia	13
Median gestational weeks in weeks (range)	
At time of referral	20 (13–30)
At first IUT	26 (18–30)
At live delivery	32 (28–36)
Maternal blood group	
O+	2
O-	5
A+	1
A-	1
B-	4
Maternal antibodies detected†	
anti-D	6
anti-D and anti-C	4
anti-K	1
anti-Js^{b}	1
None	1
Antibody titre	
1:128	1
1:512	1
1:1,024	2
1:2,048	4
>1:2,048	1
NP	2‡
Initial IUT approach	
Transplacental intravascular§	10
Intracardiac	2
Intraperitoneal	1
Mean Hb level in g/dL ± SD	
Baseline	5.2 ± 2.7
Post-IUT	12.5 ± 3.8¶
Post-delivery	10.4 ± 2.9

*HDFN = haemolytic disease of the fetus and newborn; IUFD = intrauterine fetal death; IUT = intrauterine transfusion; K = Kell; NP = not performed; Hb = haemoglobin; SD = standard deviation. *A total of 28 IUTs were performed for 13 fetuses carried by 11 women. †At time of referral. ‡Including one case with anti-K antibodies and one with non-immune HDFN due to a parvovirus infection. §Through the placental umbilical cord root. ¶Statistically significant increase in comparison to mean baseline Hb levels (P <0.01).*

according to the expected decline in Hb level, as described above.[17,22] A repeat IUT procedure was arranged if any signs of fetal anaemia developed, particularly for fetuses with features of hydrops *fetalis* at referral. The last procedure was generally performed at 34 gestational weeks, with delivery planned at >35 gestational weeks. In cases where the fetus had received an intraperitoneal transfusion, delivery was planned at 32–34 gestational weeks.

Data were analysed using the Statistical Package for the Social Sciences (SPSS), Version 22.0 (IBM Corp., Armonk, New York, USA). Descriptive statistics were calculated for continuous variables, including means, medians, standard deviations and ranges. Percentages were computed for frequency variables. Nonparametric statistical methods were employed. The correlation between gestational age at time of delivery and the number of IUT procedures performed was tested using Spearman's correlation coefficient. A Chi-squared test was used to assess the difference in outcome measures between fetuses delivered at <30 gestational weeks and those delivered at ≥30 gestational weeks. A *P* value of <0.05 was considered statistically significant.

Ethical approval for this study was obtained from the Medical Research & Ethics Committee of the College of Medicine and Health Sciences at Sultan Qaboos University (MREC #1382) and the Centre of Studies & Research at the MOH (#23/2017). In all cases, the IUT procedure was explained to the patient and informed consent was obtained prior to the transfusion.

Results

The demographic characteristics of the cases and details of the IUT procedures are shown in Table 1. During the four-year study period, 28 IUTs were performed for 13 fetuses carried by 11 women. The mean maternal age was 30.25 ± 3.40 years. Over half of the women had a gestational history of fetal anaemia causing IUFD. All cases had features of fetal anaemia at the time of presentation, while hydrops *fetalis* was present in 10 fetuses. The median gestational age at referral was 20 gestational weeks. Nine pregnancies presented with fetal anaemia at ≤22 gestational weeks, six of which were hydropic at presentation necessitating urgent transfusion. All fetuses with alloimmune-induced HDFN had very high antibody titre levels. The most common cause of immune HDFN was anti-D alloimmunisation (n = 6). Four patients had multiple antibodies (anti-D and anti-C) and only one fetus was affected by the anti-K alloantibody. There was one case of non-immune hydrops *fetalis* due to a parvovirus B19 infection diagnosed via maternal screening. Median

baseline fetal Hb levels prior to the first IUT procedure were 3.5 g/dL (range: 1.5–8.0 g/dL).

A median of two IUT procedures were required per patient (range: 1–4 procedures). There was a statistically significant difference between mean fetal Hb levels before and after the IUT procedure (5.16 ± 2.74 g/dL versus 12.48 ± 3.76 g/dL, respectively; P <0.01). The median gestational age at first IUT was 26 weeks. Of the nine pregnancies presenting with fetal anaemia at ≤22 gestational weeks, six cases were hydropic and were transfused at ≤22 gestational weeks, while the other cases presented at ≥25 gestational weeks. Of the 28 procedures, 20 were transplacental intravascular transfusions, four were transamniotic intravascular, three were intracardiac and one was intraperitoneal. Six procedures required an exchange transfusion at the beginning of the procedure due to severe fetal anaemia. None of the patients received intravenous immunoglobulin or underwent therapeutic plasma exchange prior to the IUT procedures.

The overall survival rate was 61.5%, with eight neonates surviving, including all of the non-hydropic fetuses and half of the hydropic fetuses. All four patients with multiple antibodies survived. Four of the cases of anti-D immune HDFN survived. There were five deaths, including four IUFD cases and one early neonatal death. One of the IUFDs occurred due to severe hydrops *fetalis* in a fetus transfused at ≤22 gestational weeks. Of the IUFD cases, 80% died at <30 gestational weeks. The median gestational age at the time of delivery for live fetuses was 32 gestational weeks. There was a statistically significant difference in survival rates between fetuses born at <30 gestational weeks and those born at ≥30 gestational weeks (P = 0.03). A weak correlation was also noted between gestational age at delivery and the number of IUT procedures performed; however, this difference was not statistically significant (r = 0.4; P = 0.18).

Four cases were delivered by emergency CS. Of these, one was indicated due to a procedure-related cord haematoma at 29 gestational weeks and another was indicated due to abnormal cardiotocography measurements at 30 gestational weeks. The third patient had had four previous CSs with focal placenta *accreta* in which part of the placenta attached abnormally to the myometrium and went into preterm labour. The fourth patient experienced preterm PROM leading to antepartum haemorrhage and resulting in early neonatal death. No procedure-related complications were noted in the latter three cases. The median gestational age at the time of delivery of the alive fetuses was 32 weeks (range: 28–36 weeks). Of the eight surviving fetuses, six were born at or before 32 gestational weeks. Overall, mean fetal Hb levels at birth were 10.4 ± 2.9 g/dL. All eight surviving babies were followed up by paediatricians and received phototherapy, with 87.5% requiring a top-up and/or exchange transfusion post-delivery. Two neonates suffered from neurodevelopmental delay in the early neonatal period, which resolved in one case. During the study period, one patient underwent IUT procedures during three separate pregnancies, with successful outcomes in two cases. The overall complication rate was 21%. Details of the complications and outcomes of the IUT procedures are shown in Table 2.

Discussion

To the best of the authors' knowledge, this is the first descriptive study of IUT outcomes in Oman. Other countries have similarly reported their experiences with IUT procedures.[2,9,13,14,23–26] Despite the low number of cases, the overall mortality and complication rates observed in the current study were comparable to those of initially reported rates in other research available in the literature, which range from 75% when hydrops *fetalis* is present at the start of treatment to over 90% for non-hydropic fetuses.[27] Overall, the fetal loss rate due to the procedure is 1–2%.[12,13] The mortality rate appears to be higher at gestational ages of <22 weeks (5.6%), due to the technical difficulties encountered when the procedure is performed very early in gestation.[13] The presence of hydrops *fetalis* is a major contributor to adverse outcomes. The rate of fetal death at <20 gestational weeks is higher (5.6%).[13,28] In the current study, the majority of deaths occurred among fetuses of <30 gestational weeks. This outcome is to be expected given the higher rate of prematurity-related complications in this group.

Many RBC antibodies have been implicated in immune HDFN. Most cases of severe fetal anaemia requiring *in utero* treatment are caused by anti-D, anti-C or anti-K antibodies.[29,30] Anti-D alloimmunisation is known to be associated with severe HDFN.[23] Despite ongoing efforts to prevent anti-D alloimmunisation, it remains the most common cause of HDFN.[2,9,13,14,23,24,31,32] This is consistent with the findings of the current study, in which anti-D antibodies were the most common cause of fetal anaemia necessitating IUT. This is especially concerning given the anti-D immunoglobulin policy in Oman. Al-Dughaishi *et al*. previously reported the rate of anti-D alloimmunisation in one institution in Oman to be 10%.[33] Fetal anaemia due to anti-K alloimmunisation generally develops earlier in gestation, regardless of the antibody titre level, due to the additional effect of anti-K antibodies in suppressing the erythroid precursors that express K antigens.[34] In the current study, there was one case

Table 2: Characteristics and fetal complications and outcomes among women with complications and fetal deaths after undergoing intrauterine transfusions performed in Oman over a four-year period (N = 11)

	Baseline		At first IUT				At time of complication				Outcomes	
	Cause of HDFN (titre)	Maternal history	GA in weeks	Hb level in g/dL	Presence of HF	IUT approach	GA in weeks	Number of IUTs	Complication	Prenatal/ delivery	Postnatal	Follow-up
1	anti-D (1:1024)	G6/P3/A2; 2 previous LSCS	26	3.7	No	TPI	30	3	Abnormal CTG measurements within 24 hours of the IUT	Emergency LSCS	Required TUT and PHT	Healthy at four years post-delivery
2	anti-Js[b] (1:128)	G2/P0; 2 previous IUFDs due to HF	22	1.5	Yes	TPI	29	4	Cord haematoma leading to interruption of the IUT	Emergency LSCS	Required TUT and PHT	Healthy and undergoing PT at four years post-delivery
3	anti-D (>1:2,048)	G4/P4; 4 previous LSCS with AP[†]	30	5.0	Yes	TPI	30	1	Preterm labour by LSCS due to previous LSCS history	Emergency LSCS	Required TUT and PHT; neonate had early ND *sequelae* that resolved upon follow-up	Healthy at three years post-delivery
4	anti-D (1:2,048)	G7/P4/A2; 3 previous LSCS[‡]	19	-	Yes	IP	19	1	IUFD due to severe initial HF and DC cardiac status	IUFD	-	-
5	anti-D (1:1,024)	G3/P3; 1 previous emergency LSCS due to FA[§]	25	3.0	Yes	IC	25	1	Cardiac tamponade	IUFD	-	-
9	Non-immune HF due to B19	G0/P0	20	5.0	Yes	TPI	20	1	IUFD due to severe initial HF and DC cardiac status	IUFD	-	-
10	anti-D	G2/P2; 1 previous LSCS due to HF[¶]	22	2.2	Yes	TPI	22	2	IUFD due to severe HF and DC cardiac status	IUFD	-	-
11	anti-K	G6/P5; 1 previous IUFD with HF	29	3.9	Yes	TPI	31	3	PPROM due to PHD[//]	Emergency LSCS	Neonatal death due to severe cardiac dysfunction[//]	-

IUT = intrauterine transfusion; HDFN = haemolytic disease of the fetus and newborn; GA = gestational age; Hb = haemoglobin; HF = hydrops fetalis; G = gravida; P = para; A = abortus; LSCS = low-segment Caesarean section; TPI = trans-placental intravascular; CTG = cardiotocography; TUT = top-up transfusion; PHT = phototherapy; PT = physiotherapy; AP = abnormal placentation; ND = neurodevelopmental; IP = intra-peritoneal; DC = decompensated; IUFD = intrauterine fetal death; FA = fetal anaemia; IC = intracardiac; B19 = parvovirus B19; K = Kell; PPROM = preterm premature rupture of the membrane; PHD = polyhydramnios.

[*]A total of 28 IUTs were performed for 13 fetuses carried by 11 women. [†]Of these, three neonates required PHT and one had an IUT. [‡]Of these, one pregnancy was affected by severe FA, with the fetus surviving following IUT. [§]Preterm delivery at 32 gestational weeks. [¶]Preterm delivery. [//]At 32 gestational weeks.

of anti-K-induced HDFN and hydrops *fetalis* in which the mother had a past history of IUFD due to severe hydrops *fetalis*; unfortunately, despite three IUT attempts, the neonate died due to severe cardiac dysfunction. Specialised blood bank facilities are needed in Oman for the detection and monitoring of clinically significant antibodies in such cases.

In cases with detectable antibodies, prenatal monitoring of maternal antibody titres and fetal MCA-PSV Doppler ultrasonography assessments can help to plan fetal blood sampling and IUT procedures. In general, MCA-PSV values correlate well with fetal Hb levels as a function of gestational age. The quick response of the fetal cerebral arteries to hypoxaemia—which can be determined by measuring the peak velocity of systolic blood flow using Doppler ultrasonography—is an ideal indicator of fetal anaemia.[16] Therefore, MCA-PSV measurements in fetuses at risk of anaemia due to maternal RBC alloimmunisation provide an accurate and non-invasive means of determining the severity of the anaemia, enabling the early referral of at-risk patients to specialised centres for monitoring and/or management.

The frequency of IUT procedures is determined clinically based on fetal status; in general, the interval between procedures is 2–3 weeks.[10] MCA-PSV measurements may be less accurate for the assessment of already transfused fetuses because the association between Hb levels and blood velocity is weaker in such cases. Therefore, reassessment of the need for subsequent IUTs is based on the estimated fetal Hb decrease following the initial transfusion. A previous study estimated a 1–2% decline in Hct proportion per day after an IUT procedure.[35] Therefore, in patients receiving multiple previous IUT transfusions, decisions on the timing of subsequent IUTs is made by estimating the Hb decrease in comparison to post-transfusion Hb levels after the second transfusion; the assumption is that the rate of decrease will be 0.3 g/dL per day.[17] That being said, the decision to repeat the IUT procedure should be made on an individual case-by-case basis, as an earlier procedure might be indicated if the fetus shows signs of anaemia.

The high rate of hydrops *fetalis* in the present study may reflect the late referral of patients from other centres; this supposition is also supported by the high antibody titres noted in many cases at the time of presentation. The presence of hydrops *fetalis* is a major contributor to adverse post-IUT outcomes and worsens the rate of survival.[27,28,36] Unfortunately, a comparison of survival in the current study with that reported in the existing literature was hindered by the small size of the current sample as well as the comparatively higher rate of hydrops *fetalis* at the time of patient referral which negatively affected the overall post-procedure survival rate.[27,28,36] A recent study by Zwiers *et al*. reported improved post-IUT survival at a national referral centre in New Zealand since the procedure was pioneered in 1998; this was explained by reduced severity of the disease at referral, lower rates of hydrops *fetalis* at presentation and increased Hb levels at the time of the first IUT.[23] These findings support the recommendation that high-risk pregnancies be followed up in a tertiary care centre between 15–20 gestational weeks.[24]

Overall, the complication and fetal loss rates in the current study were comparable to rates reported by other pioneer studies (0.9–4.9%).[9,37] Procedure-related fetal distress in IUT cases is usually due to either local cord complications or excessive bleeding followed by exsanguination.[13] Different approaches are utilised in transfusing fetuses and prognosis can be predicted based on the presence of hydrops *fetalis*.[32] Transfusion via a free loop of the umbilical cord is technically difficult and such an approach has been associated with increased complication rates; hence, this was not attempted in the present study.[9,13,23,24,31] Early gestational age at first transfusion is another significant risk factor for procedure-related complications, especially as performing IUTs at ≤22 gestational weeks is particularly challenging; moreover, even if the procedure is successful, many premature fetuses cannot tolerate the transfusion and therefore die *in utero*.[9,32] Fetal distress during the procedure remains one of the most critical IUD complications as this may result in preterm delivery or fetal death.[14] In the current study, only one fetus died *in utero* when transfused at ≤22 gestational weeks. Emergency CS deliveries are usually indicated due to cord complications or exsanguination following needle removal/displacement; the perinatal mortality rate for this type of delivery is estimated at 1.4–2%.[13,27,38]

In most countries, the critical antibody titre cut-off value used for fetal monitoring is 1:16, although this can vary from 1:8 to 1:32.[12,31] However, all cases of immune-induced HDFN in the current study presented with antibody titres exceeding this limit, highlighting the need for a nationwide programme for the early recognition and referral of high-risk pregnancies in Oman. Such a programme would be strengthened by the development of existing blood bank services to enhance the prompt detection of fetal antibodies and assessment of titres. Moreover, there is a need to assess compliance with existing policies regarding the antenatal and postnatal administration of anti-D immunoprophylaxis. Finally, a larger study is required to enable a comparison of Omani IUT outcomes with those reported elsewhere.

Conclusion

This study presents the first four years' experience with IUT as a life-saving pioneer procedure in Oman. Overall, this procedure appears safe and effective when carried out by a multidisciplinary team of individuals with extensive training and experience. However, access to a high-quality blood bank is necessary to ensure the availability of the required blood components, among other specialised services. Nationwide procedures for the monitoring, referral and follow-up of high-risk HDFN cases are recommended. Patients should be referred before the development of hydrops *fetalis* as this compromises post-IUT fetal survival. In the present study, the most frequent indication for IUT was due to anti-D HDFN; accordingly, compliance with existing antenatal and postnatal anti-D prophylaxis policies should be enforced to prevent anti-D alloimmunisation.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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